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Hoechst Aktiengesellschaft
Pharma Research
Toxicology

REPORT

ON

A SINGLE-DOSE ORAL TOXICITY STUDY OF H 72 6146 A
IN FEMALE SPF WISTAR RATS

October 29, 1974

Report on a
single-dose oral toxicity study of H 72 6146 A
in female SPF Wistar rats

Summary:

In this single-dose oral toxicity study of H 72 6146 A in female rats the LD₅₀ was 8100 mg per kg body weight. According to the usual classification (cf. W.S. Spector in Handbook of Toxicology), H 72 6146 A may be regarded as virtually non-toxic in a single-dose oral treatment.

Method:

Compound H 72 6146 A was available as white powder that was suspended in sesame oil. Different doses of this 25 per cent suspension were orally administered once by means of a stomach tube to female SPF Wistar rats from our own breeding. (Weight of the animals: 84 - 110 g, average weight 94 g). The study was performed in female rats, as previous studies did not reveal any sex-dependent difference in results. Each dosage group consisted of 10 rats. The rats were fasted from 16 hours prior to 2 hours after treatment. During the 2-week follow-up period the animals were weighed once weekly, and the food Altromin 1324 (mfr.: Altrogge, Lage/Lippe) and tap water were provided ad libitum.

Lethally intoxicated rats were dissected and submitted to macroscopic examination.

The surviving animals were anesthetized and killed after the 2-week follow-up period, and their organs were also examined macroscopically.

The LD₅₀ was determined by means of a probit analysis (acc. to LINDER and WEBER), and the confidence limits were calculated according to CAVALLI-SFORZA.

Results:

Dose mg/kg	Concentration in %	No. of lethally intoxicated rats/ No. of rats per dosage group
4000	25	0 out of 10
6300	25	0 out of 10
7100	25	1 out of 10
8000	25	7 out of 10
9000	25	6 out of 10
10000	25	10 out of 10
15000	25	10 out of 10

Lethally intoxicated rats showed disequilibrium, gasping respiration and in some cases tonic convulsions in abdominal position. In individual animals squatting position and hemorrhagic nasal secretion were observed. The exact time of death and data on the body weight development during the 2-week follow-up period are given in the appended Tables. The dissection of the lethally intoxicated rats revealed the following macroscopic findings:

Hemorrhagic infiltrations in sections of stomach and small intestine. Marked demarcation of blood vessels in the region of the large intestine.

The dissection of the rats that were killed at the end of the follow-up period revealed no remarkable macroscopic findings.

The median lethal dose (LD_{50}) for $P = 0.05$ was 8100 (7660 - 8570) mg H 72 6146 A per kg body weight.

Dr Ho
October 29, 1974

Pharmaceutical Research/Toxicology
of
HOECHST AG
Signed:
Dr Hollander
Dr Weigand

Appendix
3 Tables
 LD_{50} calculations

Tabelle / Table 1

H 2 6:46 A
 Akute orale Toxizität
 Ratte ♀
 29.10.1974

FARBWERKE HOECHST AG *Mannheim Ludwigshafen*

Pharma Forschung Toxikologie

Tierart: Rattus
 Species: rats

Applikationsweg:
 Route of Administration: oral, orally

Tier Nr.	Geschlecht	Dosis mg/kg	Körpergewicht (g)		
			Anfang	nach 7	nach 14 Tagen
Animal No.	Sex	Dose mg/kg	Initially	Body Weight (g) after 7	after 14 Days
1	♀	4 000	100	122	146
2			90	102	118
3			110	120	142
4			94	114	142
5			92	112	124
6			94	112	128
7			100	124	144
8			94	114	138
9			98	120	144
10			88	106	132
1	♀	6 300	88	106	128
2			86	100	124
3			90	116	142
4			90	100	126
5			92	102	134
6			90	100	122
7			94	114	142
8			90	110	140
9			88	110	128
10			94	104	124
1	♀	7 100	96	116	140
2			90	102	124
3			92	† 1./2. d.	
4			92	112	138
5			94	114	136
6			92	112	136
7			94	112	138
8			90	108	126
9			88	106	134
10			90	98	132

† Tod post applicationem
 Death after Administration / Injection



Tierart: Ratte

Species: rats

Applikationsweg:

Route of Administration: oral orally

Tier Nr.	Geschlecht	Dosis mg/kg	Körpergewicht (g)		
			Anfang	nach 7	nach 14 Tagen
Animal No.	Sex	Dose mg/kg	Initially	Body Weight (g)	
1	♀	8 000	94	± 5./6. d	
2			86	± 2./3. d.	
3			92	104	124
4			94	110	128
5			90	± 2./3. d	
6			94	± 1./2. d	
7			94	± 1./2. d	
8			94	± 5./6. d	
9			94	± 2./3. d	
10			92	108	126
1	♀	9 000	100	± 1./2. d	
2			92	± 2./3. d	
3			84	± 155 min.	
4			98	108	138
5			98	114	136
6			100	118	144
7			92	± 1./2. d	
8			94	112	142
9			96	± 1./2. d	
10			90	± 1./2. d	
1	♀	10 000	92	± 155 min.	
2			98	± 97 min.	
3			86	± 2./3. d	
4			110	± 62 min.	
5			86	± 58 min.	
6			110	± 92 min.	
7			110	± 92 min.	
8			96	± 155 min.	
9			90	± 161 min.	
10			94	± 69 min.	

† Tod post applicationem
Death after Administration / Injection

Tabelle/Table 5

FARBWERKE HOECHST AG *normaler Ratte Lucas & Brüning*

Pharma Forschung Toxikologie

H 72 6146 A
 Akute orale Toxizität
 Ratte ♀
 29.10.1974



Tierart: Ratte
 Species: rats

Applikationsweg:
 Route of Administration: oral, orally

Tier Nr.	Geschlecht	Dosis mg/kg	Körpergewicht (g)		
			Anfang	nach 7	nach 14 Tagen
Animal No.	Sex	Dose mg/kg	Initially	Body Weight (g) after 7	after 14 Days
1	♀	15 000	100	57	min.
2			94	67	min.
3			96	69	min.
4			98	51	min.
5			92	55	min.
6			92	64	min.
7			102	68	min.
8			100	55	min.
9			96	115	min.
10			98	59	min.

† Tod post applicationem
 Death after Administration / Injection

REGRESSIONSGERADE, 5%, 50%, 95% PROZ., DOSEN, VERTRAUENSGRENZEN FUER

PRAEFARAT H 726146 A SPEZIES RATTE GESCHLECHT F APPLIKATION PD VERSUCHSNR 584 DATUM 26. 7. 7

DOSIS	TIERE, GES.	TIERE, WIRKUNG	PROZENT	LOG, DOSIS	PROBIT	GEWICHT
4,000	10,	0,	0,00	1,386	0,858	0,01
6,300	10,	0,	0,00	1,861	2,579	1,31
7,100	10,	1,	10,00	1,960	3,736	4,05
8,000	10,	7,	70,00	2,079	5,504	6,34
9,000	10,	6,	60,00	2,197	5,151	5,03
10,000	10,	10,	100,00	2,303	7,174	2,08
15,000	10,	10,	100,00	2,708	9,000	0,01

GLEICHUNG DER REGRESSIONSGERADEN $y = -11,9689 + 8,1087 x$

2 PUNKTE DER REGRESSIONSGERADEN
 $x_1 = 1,39 \quad x_2 = 2,71$ {LOG, DOSIS
 $x_1 = 4,00 \quad x_2 = 15,00$ } (DOSEN)
 $y_1 = -0,72 \quad y_2 = 10,00$ {PROBITS}

DOSEN, VERTRAUENSGRENZEN		0,5 =	0,619	7,344
FUER P=0,05	5,956			
FUER P=0,01	5,793			7,590
FUER P=0,001	5,547			7,885
FUER P=0,05		0,90 =	8,103	8,565
FUER P=0,01	7,662			
FUER P=0,001	7,529			8,717
	7,378			8,896
FUER P=0,05		0,95 =	9,923	11,009
FUER P=0,01	8,944			
FUER P=0,001	8,657			11,375
	8,335			11,814